

### **REMARKS**

#### **Status of Claims and Amendment**

Claim 2 has been amended. Claims 1, 3, 6-8, 10-12, 14-15, 20-22, 24-27, 31, and 36-37 have been canceled. Claims 2, 4, 5, 9, 10, 16-19, 23, 28-30 and 32-35 are pending in the application. Claims 16-19, 23, 28-30 and 32-35 are withdrawn from consideration. Claims 2, 4, 5, 9 and 13 are under examination. Claims 2, 4, 5 and 9 are rejected.

Claim 2 has been amended to further clarify that the claimed oligonucleotide fragment is “at least 20 nucleotides in length” and that “said replacement oligonucleotide or oligonucleotide fragment binds to the same mRNA splicing product as any of said 351 oligonucleotides being replaced.” Support for the amendments to claim 2 may be found throughout the specification, for example, at page 10, line 7 and page 9, lines 10-25.

In addition, the specification at pages 44, 75, 76, 77, 88, 89, 96, 102, 103, and 106 have been amended to correct for minor typographical errors.

No new matter is added.

#### **Information Disclosure Statements**

Applicants thank the Examiner for acknowledgement of the Information Disclosure Statement filed October 2, 2007 by returning a signed and initialed copy of the PTO Form SB/08 submitted therewith. The Examiner has indicated consideration of Liew et al., Cheung et al., Wu et al., and Newton et al. However, the Examiner has again not considered the Fujioka reference on the PTO Form SB/08, indicating that a copy of the reference was not provided.

In response, Applicants submit herewith a copy of the Fujioka reference. Furthermore, Applicants submit herewith Whitney et al., PNAS 100(4): 1896-1901 (2003) which was cited in an Official Office Action dated October 30, 2008 of a co-pending European patent application. Applicants note that Whitney was cited by the EPO without any specific objections made against the claimed invention. In this regard, Applicants note that Whitney is directed to variability in gene expression in normal human blood samples to provide a database against which disease-associated gene expression patterns could be compared. However, Whitney does not disclose the claimed oligonucleotide probes, nor analysis of disease samples.

The Examiner is respectfully requested to acknowledge and indicate consideration of Fujioka and Whitney by returning a signed and initialed copy of the PTO Form SB/08 submitted herewith.

#### **Response to Notice for Sequence Compliance**

At page 3 of the Office Action, the Examiner maintains the objection that the Sequence Listing fails to comply with C.F.R. §§ 1.821(c) and (d). The Examiner asserts that the Sequence Listing only contains SEQ ID NOs:1-501, but the specification contains sequences that are not included in the Sequence Listing. For instance, the Examiner notes that page 89, line 1 refers to SEQ ID NO 1231, and the Tables in the specification contain numerous SEQ ID NOs that correspond to nucleic acid sequences other than the 501 sequences listed in the Sequence Listing. In addition, the Examiner notes that page 166 refers to "Sequence ID 502", and page 278 refers to "SEQ ID NO: 1495" and SEQ ID NO: G6 which is an improper sequence identifier.

The Examiner requires that Applicants check the disclosure for any other nucleic acid or protein sequences and list them in the Sequence Listing with a proper SEQ ID NO.

The Examiner further asserts that the specification and Sequence Listing must be amended to be compliant.

In response, Applicants note that the Substitute Specification filed October 3, 2008 addressed this matter. In this regard, pages 72-123 and pages 124-279 of the original specification have been amended to correspond to the respective SEQ ID NOs listed in the Sequence Listing of May 1, 2006. Because all the sequences disclosed in the specification correspond to the respective SEQ ID NOs in the Sequence Listing, the Sequence Listing contains all the sequences disclosed in the specification, and is in compliance with C.F.R. §§ 1.821(c) and (d). Thus, the objection should be withdrawn, as the previous amendments to the specification should have been entered despite the new matter rejection to the specification set forth below.

Withdrawal of the grounds of objection is respectfully requested.

**Response to Objections to the Specification Under 35 U.S.C. § 132(a)**

The amendments to the specification filed October 3, 2008 are objected to under 35 U.S.C. 132(a) because the amendment allegedly introduces new matter into the disclosure.

The Examiner asserts that numerous SEQ ID NOs associated with each clone ID have been changed so that the clone ID of the specification now corresponds to different SEQ ID NOs. For example, the Examiner asserts that clone ID I-24 was previously listed as corresponding to SEQ ID NO: 308. However, in the amended Table 1a, clone ID I-24 is listed as corresponding to SEQ ID NO: 11. The Examiner asserts that although SEQ ID NOs: 11 and 308

have the same number of nucleotides they have different sequences. Furthermore, the Examiner asserts the amendment of October 3, 2008 lists clone ID V-61 as SEQ ID NO: 308 but the specification of May 19, 2005 lists clone ID V-61 as SEQ ID NO 721. In view of the above, the Examiner asserts that the amendment is not supported by the original disclosure.

Furthermore, the Examiner asserts that Tables 1a, 2b, 3, 4a, 4b and 9 have deleted references to a number of clones and/or have changed the SEQ ID NOs associated with each clone ID. The Examiner asserts that because the deletion of clone ID NOs and changes in SEQ ID NOs are neither an obvious error nor an obvious correction, the amendments constitute new matter. Further, the Examiner appears to assert that the deletion of certain clone IDs indicated as informative for disease diagnosis in the specification of May 19, 2005, changes the scope of the disclosure.

As discussed above, and in the Amendment filed October 3, 2008, Applicants note that a Sequence Listing was filed May 1, 2006 containing all the sequences disclosed in the original specification. The Sequence ID numbers listed in the original specification were not in consecutive order, starting at 93 and ending at 1495 (with many numbers missing in between). Additionally, Sequence IDs G6, 61, 490, 892 and 77 appeared at the end of the otherwise numerically increasing list. Subsequently a Sequence Listing was filed on May 1, 2006 in which the sequences were presented in a consecutive list of 501 sequences, but the sequences in the specification were inadvertently not amended at the same time to correspond to the list of 501 sequences. The Substitute Specification filed October 3, 2008 was merely provided to remedy

this matter so that the original sequences disclosed correspond to the SEQ ID NOs in the Sequence Listing of May 1, 2006.

Further, the Tables at pages 72-121 were amended to remove the sequences that were indicated as “missing” because these sequences are technically not missing insofar as there were no actual sequences provided in the original disclosures at pages 124-279 or the original Sequence Listing submitted. Also, Applicants note that as disclosed, for instance, at page 8, lines 24-27 of the original specification, it is stated that preferred oligonucleotides of the present invention are those for which sequences are provided. This disclosure concerns Table 1, which is a composite of the probes of the other tables. As indicated on page 7, line 36 to page 8, line 1, preferred oligonucleotides are as described in Table 2 or 4, and on page 6, lines 18-21, Table 2 refers to Table 2a and/or Table 2b. Accordingly, pursuant to M.P.E.P. § 2163.07, one of ordinary skill in the art would understand from reading the disclosure in the specification, that the specification that the claimed probe encompasses the probes in Table 2b, for which sequences are provided. Thus, no new matter is added by removing sequences for which no sequences have been provided.

Accordingly, removal of the columns and rows indicating “missing” does not constitute new matter for removal of sequences because no actual sequences were provided in the original disclosures for the columns and rows indicating “missing”.

Withdrawal of the grounds of objection is respectfully requested.

**Response To Claim Rejection Under 35 U.S.C. § 112 For Enablement**

Claims 2, 4-5, 9 and 13 are rejected under 35 U.S.C. § 112, first paragraph, for lack of

enablement, for the reasons of record.

Initially, the Office Action asserts that amended claim 2 broadly encompasses replacing the claimed oligonucleotide probes with (i) “any” oligonucleotide fragment thereof in which the fragment is at least 15 nucleotides in length, (ii) any oligonucleotide that is complementary to the claimed SEQ ID NO or any fragment that is at least 10 nucleotides in length, and (iii) an oligonucleotide having at least 80% identity to the replaced nucleotide or a fragment thereof that is at least 10 nucleotides in length.

The Office Action asserts that for the specification to be enabling for the claimed oligonucleotide probes, the specification must teach how to use the claimed probe set for diagnosis of disease.

Although the Office Action acknowledges that gene expression between healthy and diseased individuals may be predictably compared,<sup>1</sup> the Office Action appears to assert that Applicants’ arguments are not persuasive because one of ordinary skill in the art would not be able to predictably associate the changes with the disease states due to the new matter objection discussed above and the breadth of the present claims. Specifically, the Office Action appears to assert that (1) the specification does not disclose the claimed combination of probes that are informative for the diagnosis of disease states, and (2) the claims are not limited to sequences disclosed, but also encompass fragments and fragments with a certain percent identity so that it would be unpredictable to diagnose cancer based on these claimed fragments.

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<sup>1</sup> See page 18, lines 6-7 of the present Office Action. The Office Action also acknowledges that normalization and background subtraction are common and done in the art. See page 18, lines 11-12 of the present Office Action.

The Office Action's assertions with regard to (1) appear to be related to the new matter objection to the specification discussed above. That is, the Office Action appears to assert that Applicants' arguments that Table 2b encompasses the claimed probes is not persuasive since it is unclear to the Office Action which probes are informative in view of the new matter objection to the specification.<sup>2</sup> In this regard, the Office Action asserts that Table 2 submitted on May 19, 2005 did not recite the combination of claimed SEQ ID NOs, but the specification submitted on October 3, 2008 contains the claimed SEQ ID NOs.

The Office Action asserts that Applicants' arguments regarding Example 3 and the Rule 132 Declaration by Dr. Praveen Sharma explaining Example 3 of the specification is not persuasive because of the statement that "[t]he use of the 345 probes in Example 3 is not significantly different from the use of the claimed 351 probes." (See page 20, lines 2-7 of the present Office Action). The Office Action asserts that such a statement suggests that Example 3 does not use the claimed probes. Further, the Office Action asserts that arguments that use of probes of approximately the same size would not impact the outcome is not persuasive because the claims encompass fragments and fragments with a certain percent identity, which depending on the probe being examined, could be any nucleic acid sequence. This aspect of the rejection is related to the Office Action's contentions concerning the scope of the claims mentioned in (2)

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<sup>2</sup> The Office Action appears to assert it is unpredictable to use the claimed 351 probes to detect breast cancer or Alzheimer's when the specification teaches probe sets that are larger and range from 1435 probes to 730 probes. The Office Action asserts that the specification does not disclose the probes required for diagnosis or the use of the claimed probes for diagnosis. The Office Action asserts that the amended specification has changed the SEQ ID NOs associated with the clone ID as well as deleted over 100 clone IDs that were previously indicated as informative, which suggests that the initial disclosed clone ID and probes are not predictable.

above.

Further, the Office Action asserts that Applicants' arguments that 139 informative probes are selected for breast cancer diagnosis and 192 probes are selected for Alzheimer's diagnosis are not persuasive because although Table 7 lists the 139 probes used for breast cancer, Table 7 does not teach the sequences used and teaches a 20% error rate. Similarly, the Office Action asserts Table 2a does not disclose the sequences of the 77 probes listed.

The Office Action then appears to address Applicants' citation of Orr<sup>3</sup> by citing Draghici to support the position that there is unpredictability in using arrays that have not been verified for clinical use. Accordingly, the Office Action asserts that performing the microarray analysis is not the issue. Rather, the issue is asserted by the Office Action to be whether breast cancer or Alzheimer's disease may predictably be detected based on array data, when neither the specification nor the art has identified the claimed sequences to be involved in identifying these diseases.

With regard to (2), the Office Action appears to assert that the specification does not provide examples of replacing any SEQ ID NOs with fragments of the cited SEQ ID NOs or sequences that are 80% identical to the fragments.

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<sup>3</sup> Although Orr is cited by Applicants to show that large-scale gene expression analysis is known and routinely used in clinical biological arts for diagnosis of disease, the Office Action finds this argument to be not persuasive because Orr is a review article directed to identifying differential regulation of genes in cell culture in response to a drug. The Office Action appears to assert that the system used in Orr is of a different scope than the presently claimed invention which examines subtle differences in gene expression for a disease over time. Also, the Office Action appears to assert that Orr teaches that it is unpredictable to use an array without verification because of the lack of agreement between message and protein levels in certain cases. (See page at page 15-16 of the Office Action).



In response, with regard to (1), Applicants note that because it appears this aspect of the rejection is directly connected to the new matter objection raised by the Office Action regarding the amendments made in the Substitute Specification filed October 3, 2008, Applicants believe the explanation provided above and the previous amended specification clarifies that the specification discloses the claimed combination of probes that are informative for the diagnosis of disease states. That is, in the amendments made in the Substitute Specification all the sequences disclosed in the specification correspond to the respective SEQ ID NOs in the Sequence Listing, and the Sequence Listing contains all the sequences disclosed in the specification, which is in compliance with C.F.R. §§ 1.821(c) and (d). Accordingly, as previously argued, the presently claimed probes are the probes disclosed in Table 2b. The presently claimed probes have already been identified as being differentially expressed in breast cancer versus normal samples, and thus offers the selection of probes to be used in the present invention. The specification illustrates that the claimed probes may be used for the diagnosis of breast cancer. Accordingly, because one of ordinary skill in the art would understand and is informed from reading the disclosure in the specification, which probes may be used for breast cancer diagnosis, one of ordinary skill in the art would be enabled to practice the presently claimed invention.

In relation to Example 1, and contrary to the Office Action's comments that 938 genes were used to identify breast cancer, 139 genes were found to be informative (page 54, lines 3-5; page 55, lines 9-13 and Table 6, last row of specification) and 44 were used for the classification shown in Figure 2. Figure 2 shows a correct classification of most normal and breast cancer women into their

respective groups. The Office Action also points to Table 6 asserting that between 23 and 139 probes were used diagnostically with an error of 13 to 20%. However, contrary to the Office Action's assertions, Table 6 shows that variable numbers of probes can be used and even when very similar error rates were observed, even genes of lower occurrence are found to be informative in 80% of cases. This therefore shows that the specific selection of probes to be used for diagnosis from the lists provided, may be varied.

Furthermore in relation to Example 2, although the Office Action states that 758 probes were used, in fact 182 probes were used for classification as shown in Figure 3 (and page 54, lines 5-6 of specification). The 758 probes were used as the pool from which to select the informative probes. The results of Table 7 are entirely misinterpreted by the Office Action. Those results reflect classification of further samples using the 182 informative probes as used in Figure 3 and do not, as the Office Action suggests, fail to predict Alzheimer's for any of the 14 subjects analyzed. Instead, the results clearly show that the false positive rate was zero and the false negative rate was 14% indicating that only one of the 14 patients was incorrectly diagnosed and this is clearly indicated in the panel referring to the validation results.

With regard to Example 3, the Office Action appears to assert that a classification model is generated using 719 probes. However, the analysis was additionally conducted with 111 (page 69, lines 30-31 and Figures 6 and 7 of specification) or 345 probes (page 69, lines 32-33, Figures 8 and 9 of specification).

On page 20 of the Official Action the Office Action discusses Applicants' reference to Example 3 to support the use of the claimed 351 probes since 345 probes are used in Example 3.

Applicants note that the 345 probes used in Example 3 are encompassed by the claimed 351 probes. Thus, the claimed set includes an additional 6 probes. However, over 98% of the probes are identical. In view of the large number of probes in use and the fact that the probes used in Example 3 are almost identical to those as claimed, it is evident that there would be little significant impact on the outcome or reliability of the classification model for diagnosis. As discussed above, some variation on the selection of specific probes is tolerated. Thus, Example 3 is supportive of the presently claimed embodiment in which the 351 specifically recited probes are used. The utility of the Example 3 probes were previously discussed on page 27 of the Amendment filed October 3, 2008.

The previously submitted Rule 132 Declaration illustrates that the claimed 351 probes may be used for diagnosing breast cancer, and that the method was performed as in Example 1. Thus the expression pattern for the 351 probes was used for classification purposes. The expression pattern was obtained by binding mRNA from breast cancer samples to those probes. This in effect corresponds to the test gene transcript pattern generation. Methods of preparing standard gene transcript patterns are covered in the earlier steps in which probes are identified as those which are informative and the generation of a classification model which is in effect the standard gene transcript pattern for comparison purposes. Accordingly, the 345 probes shown to be useful for the diagnosis of breast cancer is sufficiently representative of the presently claimed 351 oligonucleotide probes. The fact that the addition of 6 further probes has little if any effect on efficacy has been borne out in practice and the results of adding these probes are presented in the previously submitted Rule 132 Declaration.

Thus, the specification, as evidenced by the Declaration, enables the use of the presently claimed 351 probes for the prediction of breast cancer and normal samples. The results are in line with the results shown for Example 3 in the specification.

Therefore, the previously submitted Rule 132 Declaration demonstrates the use of the claimed probes in diagnosing breast cancer, as shown in Figures 1 and 2 of the specification and commensurate with the results of Example 3. One of ordinary skill in the art would understand how to use the claimed oligonucleotides to diagnose diseases of interest based upon the standard and test gene transcript pattern obtained from binding to the claimed probes.

The Office Action also identifies that there are no examples using fragments or related sequences (page 10, lines 8-9 of the Official Action). Further the Office Action asserts that in at least two sequences there are long stretches which have degenerate nucleotides (page 10, lines 10-15 of the Official Action), then citing Cheung, Wu and Newton. As previously argued, Cheung, Wu, and Newton<sup>4</sup> are not relevant since the specific probes of interest have already been identified, as presently claimed. Accordingly, because the probes to be used have already been identified as claimed, by reference to their sequences, difficulties in their identification is irrelevant. Furthermore, the specification identifies probes to identify transcripts which provide a "fingerprint" useful for diagnosing the disease. The use of fragments and related sequences will still identify the same transcripts and therefore still allow assessment of whether the relevant

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<sup>4</sup>Cheung and Wu are merely concerned with identifying informative genes, which has already been performed and provided in the present invention. Similarly, Newton shows that variation exists in the level of expression, but also teaches how to identify significant variation which is more relevant to identifying genes than working with the genes once the genes have been identified.

transcript fingerprint is present. These fragments and related sequences have been further limited to those which bind to the same mRNA. Thus, the presently claimed replacement oligonucleotide probes are effective and the oligonucleotide fragments have the same functional effect because the probes bind to the same mRNA splicing product as any of the 351 oligonucleotides being replaced. Thus Cheung, Wu, and Newton are irrelevant since the probes of relevance have already been identified and shown to be useful.

With respect to Orr, Applicants note that Orr teaches the use of microarray analysis for discovery of candidate drug targets, as well as discovery of novel diagnostic markers to help improve disease detection and treatment.<sup>5</sup> Furthermore, Orr teaches that once a gene of interest is established as differentially expressed in a particular disease phenotype, further characterization of that gene by standard molecular biology methods is often performed. (See page 476, 1<sup>st</sup> column, 2<sup>nd</sup> full paragraph of Orr). Thus, “[t]he fact experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.” M.P.E.P. §2164.01. Additionally, Orr discloses that the ability to use gene expression databases from diverse model systems will enable researchers to identify cells that contain newly discovered genes of interest in a time efficient manner. In particular, Orr teaches that tissue microarrays allow for rapid determination of target gene expression levels in as many as 1000 different tissue biopsies. (See page 476, 2<sup>nd</sup> column). Thus, Orr teaches that large-scale gene expression analysis is well-known and routinely used in the clinical biological arts for

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<sup>5</sup> “[A]n abundance of candidate drug targets and diagnostic markers are currently being discovered by microarray analysis.” See page 476, 2<sup>nd</sup> column of Orr.

diagnosis of disease states from clinical samples of tissues or cells originating from diseased tissues or cells.

With regard to Draghici, and contrary to the Office Action's contention that there is unpredictability in using arrays that have not been verified for clinical use, Applicants note that Draghi explicitly recognizes that "a multi-genic classifier based on prior biological knowledge and extracted from the literature can be predictive in a given microarray data set [emphasis added]." See page 102, Box 2, 1<sup>st</sup> column, 2<sup>nd</sup> full paragraph to 2<sup>nd</sup> column, 1<sup>st</sup> full paragraph of Draghici. Pursuant to M.P.E.P. § 2164.03, "[i]f one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art."

In summary, Applicants note that Claim 2 is drawn to several embodiments. The first embodiment is the use of each of the 351 recited oligonucleotides precisely in the form in which they are presently recited. The Office Actions's objection to this aspect of the claimed invention appears to be that Applicants have provided no evidence that this combination of probes allows for the diagnosis of any disease. In response, Applicants note that the probes are clearly fully described so that the one of ordinary skill in the relevant art possessing common technical knowledge of the art, would understand from reading the specification that the presently claimed probes are informative. Further, the functional utility of the claimed probes for diagnostic tests has been demonstrated in both the specification and the previously submitted Rule 132 Declaration. The Office Action from the bottom of page 17 appears to assert that the specification only teaches larger probe sets with from 730 to 1435 probes. As discussed above,

the Office Action has clearly misinterpreted how some of the Examples were performed and Applicants have illustrated that smaller probe families may be used diagnostically.

Accordingly, the specification provides ample disclosure and guidance to enable one of ordinary skill in the art to use the claimed oligonucleotides, for example, in a microarray or macroarray to diagnose disease states such as cancer and/or Alzheimer's disease. Based upon the disclosure in the specification, one of ordinary skill in the art would be enabled to use the presently claimed set of oligonucleotide probes with the proviso that any of said 351 oligonucleotides may be replaced in said set with (i) an oligonucleotide fragment of the respective oligonucleotide being replaced, which fragment is at least 20 nucleotides in length, (ii) an oligonucleotide having a sequence entirely complementary to the respective oligonucleotide being replaced, or to a fragment thereof which is at least 20 nucleotides in length, or (iii) an oligonucleotide having at least 80% identity to the respective oligonucleotide being replaced or to a fragment thereof which is at least 20 nucleotides in length, wherein said replacement oligonucleotide or oligonucleotide fragment binds to the same mRNA splicing product as any of said 351 oligonucleotides being replaced.

Thus, the presently claimed fragments and replacement oligonucleotides must bind to the same mRNA splicing product as the respective oligonucleotide being replaced. Accordingly, one or more of the presently claimed 351 oligonucleotide probes may be replaced, but the replacement oligonucleotide is functionally equivalent to the claimed 351 oligonucleotide because the claimed fragments and replacement oligonucleotides must still identify the same mRNA splicing product.

Reconsideration and withdrawal of the rejection under § 112, first paragraph, is respectfully requested.

**Response To Claim Rejections Under 35 U.S.C. § 102**

Claims 2, 4, 9, and 13 are rejected under 35 U.S.C. § 102(b) as being anticipated by Ahr et al ( Journal of Pathology (2001) volume 195, pages 312-320), for the reasons of record.

The Office Action appears to base this rejection on similar reasons as those discussed above under the enablement rejection. Namely, that the claims are not structurally limited to only the 351 probes claimed because the 351 oligonucleotides may be replaced with an oligonucleotide fragment of the respective oligonucleotide or an oligonucleotide fragment having at least 80% identity to the respective oligonucleotide. Accordingly, because the Office Action believes the claimed probes may encompass “any” oligonucleotide fragment, claim 2 is asserted to broadly encompass any nucleic acid sequence.

In addition, the Office Action asserts that Applicants’ arguments are not persuasive because the claims are not limited to the disclosed sequences, as discussed above. Thus, the Office Action asserts that because the claims require at least 351 oligonucleotides and less than 1000 oligonucleotides, the claimed oligonucleotides may be any sequence and are anticipated by Ahr.

In response, Applicants note that Ahr does not explicitly or inherently disclose the presently claimed set of oligonucleotide probes with the proviso that any of said 351 oligonucleotides may be replaced in said set with (i) an oligonucleotide fragment of the respective oligonucleotide being replaced, which fragment is at least 20 nucleotides in length, (ii)



an oligonucleotide having a sequence entirely complementary to the respective oligonucleotide being replaced, or to a fragment thereof which is at least 20 nucleotides in length, or (iii) an oligonucleotide having at least 80% identity to the respective oligonucleotide being replaced or to a fragment thereof which is at least 20 nucleotides in length, wherein said replacement oligonucleotide or oligonucleotide fragment binds to the same mRNA splicing product as any of said 351 oligonucleotides being replaced.

Reconsideration and withdrawal of the rejection under § 102(b) is respectfully requested.

### **Conclusion**

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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